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Cancer Vaccine Fact Sheet

Key Points

- Cancer vaccines are intended either to treat existing cancers (therapeutic vaccines) or to prevent the development of cancer (prophylactic vaccines). (Question 1)
- Therapeutic vaccines, which are administered to cancer patients, are designed to treat cancer by stimulating the immune system to recognize and attack human cancer cells without harming normal cells. Prophylactic vaccines are given to healthy individuals to stimulate the immune system to attack cancer-causing viruses and prevent viral infection. (Questions 1 and 3)
- At this time, two vaccines have been licensed by the U.S. Food and Drug Administration to prevent virus infections that can lead to cancer: the hepatitis B vaccine, which prevents infection with the hepatitis B virus, an infectious agent associated with liver cancer; and Gardasil™, which prevents infection with the two types of human papillomavirus that together cause 70 percent of cervical cancer cases worldwide. (Question 2)
- Scientists are currently evaluating several different vaccines in large human trials to determine which approaches are most effective for particular kinds of cancers. (Questions 6, 10 and 11)

1. What is a cancer vaccine?

Cancer vaccines are intended either to treat existing cancers (therapeutic vaccines) or to prevent the development of cancer (prophylactic vaccines). Both types of vaccines have the potential to reduce the burden of cancer. Treatment or therapeutic vaccines are administered to cancer patients and are designed to strengthen the body's natural defenses against cancers that have already developed. These types of vaccines may prevent the further growth of existing cancers, prevent the recurrence of treated cancers, or eliminate cancer cells not killed by prior treatments. Prevention or prophylactic vaccines, on the other hand, are administered to healthy individuals and are designed to target cancer-causing viruses and prevent viral infection.

2. What cancer-related vaccines are currently available in the United States?

At this time, two vaccines have been licensed by the U.S. Food and Drug Administration to prevent virus infections that can lead to cancer: the hepatitis B vaccine, which prevents infection with the hepatitis B virus, an infectious agent associated with some forms of liver cancer; and Gardasil™, which prevents infection with the two types of human papillomavirus (HPV) - HPV 16 and 18 -- that together cause 70 percent of cervical cancer cases worldwide. Gardasil also protects against infection with HPV types 6 and 11, which account for 90 percent of cases of genital warts.

There are no licensed therapeutic vaccines to date. However, several treatment vaccines are in large-scale testing in humans.

3. How are therapeutic vaccines designed to treat cancer?

Vaccines used to treat cancers take advantage of the fact that certain molecules on the surface of cancer cells are either unique or more abundant than those found on normal or non-cancerous cells. These molecules, either proteins or carbohydrates, act as antigens, meaning that they can stimulate the immune system to make a specific immune response. Researchers hope that when a vaccine containing cancer-specific antigens is injected into a patient, these antigens will stimulate the immune system to attack cancer cells without harming normal cells.

4. Why does the immune system need a vaccine to help fight cancer?

The immune system generally doesn't "see" tumors as dangerous or foreign, and doesn't mount a strong attack against them. One reason tumor molecules do not stimulate an effective immune response may be that tumor cells are derived from normal cells. Therefore, even though there are many molecular differences between normal cells and tumor cells, cancer antigens are not truly foreign to the body, but are normal molecules, either altered in subtle ways or more abundant.

Another reason tumors may not stimulate an immune response is that cancer cells have developed ways to "escape" from the immune system. Scientists now understand some of these modes of escape, which include shedding tumor antigens, and reducing the number of molecules and receptors that the body normally relies on to activate T cells (specific immune cells) and other immune responses. Reducing these molecules makes the immune system less responsive to the cancer cells; the tumor becomes less "visible" to the immune cells. Scientists hope that this knowledge can be used by researchers to design more effective vaccines.

5. What strategies are used to design effective cancer treatment vaccines?

Researchers have developed several strategies to stimulate an immune response against tumors. One is to identify unusual or unique cancer cell antigens that are rarely present on normal cells. Other techniques involve making the tumor-associated antigen more immunogenic, or more likely to cause an immune response, such as (a) altering its amino acid structure slightly, (b) placing the gene for the tumor antigen into a viral vector (a harmless virus that can be used as a vehicle to deliver genetic material to a targeted cell), and (c) adding genes for one or more immuno-stimulatory molecules into vectors along with the genes for the tumor antigen. Another technique is to attach something that is clearly foreign, known as an adjuvant, to tumor molecules (see Question 8). By using the adjuvant as a decoy, the immune system may be "tricked" into attacking both the antigen/adjuvant complex (the vaccine) and the patient's tumor.

6. What types of treatment vaccines are currently under investigation?

The types of vaccines listed below represent various methods investigators have devised for presenting cancer antigens to the body's immune system. This list is not meant to be comprehensive.

Antigen/adjuvant vaccines
Antigen vaccines were some of the first cancer vaccines investigated. Antigen vaccines commonly use specific protein fragments, or peptides, to stimulate the immune system to fight tumor cells. One or more cancer cell antigens are combined with a substance that causes an immune response, known as an adjuvant. A cancer patient is vaccinated with this mixture. It

is expected that the immune system, in responding to the antigen-carrying adjuvant, will also respond to tumor cells that express that antigen.

Whole cell tumor vaccines
Taken either from the patient's own tumor (autologous) or tumor cells from one or more other patients (allogeneic), these whole cell vaccine preparations contain cancer antigens that are used to stimulate an immune response.

Dendritic cell (DC) vaccines
Specialized white blood cells, known as dendritic cells (DCs), are taken from a patient's blood through a process called leukapheresis. In the laboratory, the DCs are stimulated with the patient's own cancer antigens, grown in petri dishes, and re-injected into the patient. Once injected, DC vaccines activate the immune system's T cells. Activation by DCs is expected to cause T cells to multiply and attack tumor cells that express that antigen.

Viral vectors and DNA vaccines
Viral vectors and DNA vaccines use the nucleic acid sequence of the tumor antigen to produce the cancer antigen proteins. The DNA containing the gene for a specific cancer antigen is manipulated in the laboratory so that it will be taken up and processed by immune cells called antigen-presenting cells (APCs). The APC cells then display part of the antigen together with another molecule on the cell surface. The hope is that when these antigen-expressing APC cells are injected into a person, the immune system will respond by attacking not only the APC cells, but also tumor cells containing the same antigen. Vector-based and DNA vaccines are attractive because they are easier to manufacture than some other vaccines.

Idiotype vaccines
Because antibodies contain proteins and carbohydrates, they can themselves act as antigens and induce an antibody response. Antibodies produced by certain cancer cells (i.e., B-cell lymphomas and myelomas), called idiotype antibodies, are unique to each patient and can be used to trigger an immune response in a manner similar to antigen vaccines.

7. **Which antigens are commonly found in cancer vaccines under investigation?**

Cancer cell antigens may be unique to individual tumors, shared by several tumor types, or expressed by the normal tissue from which a tumor grows. In 1991, the first human cancer antigen was discovered in the cells of a patient with metastatic melanoma, a potentially lethal form of skin cancer. The discovery led to a flurry of research to identify antigens for other cancers.

Treatment Vaccines

Patient-specific vaccines use a patient's own tumor cells to generate a vaccine intended to stimulate a strong immune response against an individual patient's malignant cells. Each therapy is tumor-specific so, in theory, cells other than tumor cells should not be affected. There are several kinds of patient-specific vaccines under investigation that use antigens from a patient's own tumor cells.

Prostate Specific Antigen (PSA) is a prostate-specific protein antigen that can be found circulating in the blood, as well as on prostate cancer cells. PSA generally is present in small amounts in men who do not have cancer, but the quantity of PSA generally rises when prostate cancer develops. The higher a man's PSA level, the more likely it is that cancer is present, but there are many other possible reasons for an elevated PSA level. Patients have been shown to mount T-cell responses to PSA.

Sialyl Tn (STn) is a small, synthetic carbohydrate that mimics the mucin molecules (the primary molecule present in mucus) found on certain cancer cells.

Heat Shock Proteins (HSPs) (e.g., gp96) are produced in cells in response to heat, low sugar levels and other stress signals. In addition to protecting against stress, these molecules are also involved in the proper processing, folding, and assembling of proteins within cells. In laboratory experiments, HSPs from mouse tumors, in combination with small peptides, protected mice from developing cancer. The human vaccine consists of heat shock protein and associated peptide complexes isolated from a patient's tumor. HSPs are under investigation for treatment of several cancers including liver, skin, colon, lung, lymphoma and prostate cancers.

Ganglioside molecules (e.g., GM2, GD2, and GD3) are complex molecules containing carbohydrates and fats. When ganglioside molecules are incorporated into the outside membrane of a cell, they make the cell more easily recognized by antibodies. GM2 is a molecule expressed on the cell surface of a number of human cancers. GD2 and GD3 contain carbohydrate antigens expressed by human cancer cells.

Carcinoembryonic antigen (CEA) is found in high levels on tumors in people with colorectal, lung, breast and pancreatic cancer as compared with normal tissue. CEA is thought to be released into the bloodstream by tumors. Patients have been shown to mount T-cell responses to CEA.

MART-1 (also known as **Melan-A**) is an antigen expressed by melanocytes – cells that produce melanin, the molecule responsible for the coloring in skin and hair. It is a specific melanoma cancer marker that is recognized by T cells and is more abundant on melanoma cells than normal cells.

Tyrosinase is a key enzyme involved in the initial stages of melanin production. Studies have shown that tyrosinase is a specific marker for melanoma and is more abundant on melanoma cells than normal cells.

Prevention Vaccines

Viral proteins on the outside coat of cancer-causing viruses are commonly used as antigens to stimulate the immune system to prevent infections with the viruses.

8. **What are adjuvants? Which adjuvants are commonly used in treatment vaccines?**

To heighten the immune response to cancer antigens, researchers usually attach a decoy substance, or adjuvant, that the body will recognize as foreign. Adjuvants are weakened proteins or bacteria which "trick" the immune system into mounting an attack on both the decoy and the tumor cells. Several adjuvants are described below:

Keyhole limpet hemocyanin (KLH) is a protein made by a shelled sea creature found along the coast of California and Mexico known as a keyhole limpet. KLH is a large protein that both causes an immune response and acts as a carrier for cancer cell antigens. Cancer antigens often are relatively small proteins that may be invisible to the immune system. KLH provides additional recognition sites for immune cells known as T-helper-cells and may increase activation of other immune cells known as cytotoxic T-lymphocytes (CTLs).

Bacillus Calmette Guerin (BCG) is an inactivated form of the tuberculosis bacterium. BCG is added to some cancer vaccines with the hope that it will boost the immune response to the vaccine antigen. It is not well understood why BCG may be especially effective for eliciting immune response. However, BCG has been used for decades with other vaccines, including the vaccine for tuberculosis.

Interleukin - 2 (IL-2) is a protein made by the body's immune system that may boost the cancer-killing abilities of certain specialized immune system cells called natural killer cells. Although it can activate the immune system, many researchers believe IL-2 alone will not be enough to prevent cancer relapse. Several cancer vaccines use IL-2 to boost immune response

to specific cancer antigens.

Granulocyte Monocyte-Colony Stimulating Factor (GM-CSF) is a protein that stimulates the proliferation of antigen-presenting cells.

QS21 is a plant extract that, when added to some vaccines, may improve the body's immune response.

Montanide ISA-51 is an oil-based liquid intended to boost an immune response.

9. **Why are some vaccines used to treat specific kinds of cancer?**

Many cancer vaccines treat only specific types of cancers because they target antigens found on specific cancers. For example, a vaccine against prostate cancer may be able to attack cancer cells within the prostate itself or cells that have spread to other parts of the body, but would not affect cancers originating in other tissues.

Vaccines that target antigens found on several different kinds of cancer cells are used to treat multiple cancers. The effectiveness of the vaccine would be expected to differ according to the amount of antigen on different kinds of cancer cells. Researchers also are investigating a possible "universal" cancer vaccine that might cause an immune response against cancer cells that originate from any tissue.

10. **Are there other vaccines under development to prevent cancer?**

Yes, in addition to the FDA-approved Hepatitis B vaccine and HPV vaccine, there are other vaccines currently under investigation that have the potential to reduce the risk of cancer. These vaccines target infectious agents that cause cancer, similar to traditional prophylactic vaccines that target other disease-causing infectious agents, such as those that cause polio or measles. Non-infectious components of cancer-causing viruses, commonly the viral coat proteins (proteins on the outside of the virus), serve as antigens for these vaccines. It is hoped that these antigens will stimulate the immune system in the future to attack cancer-causing viruses, which should, in turn, reduce the risk of the associated cancer.

11. **Which vaccines have reached Phase III testing?**

The results from ongoing or unpublished Phase III trials, listed in the table below, will determine what role vaccines will play in the treatment and prevention of different cancers. The information is derived from government databases including the National Cancer Institute's clinical trials database, http://cancer.gov/clinicaltrials/search, and the National Institutes of Health clinical trials Web site, http://clinicaltrials.gov. Information about each trial also can be obtained by clicking the links in the far right column of the table.

Phase III Vaccine Trials

Type of Cancer	Title of Study	Vaccine Name (if applicable)	Lead Institution	Nature of Vaccine	Purpose of the Study	Study Start Date, Links, and Status
Cervical Cancer		Gardasil™ HPV (human papilloma virus) quadrivalent vaccine	Merck & Co.	The HPV quadrivalent vaccine contains viral proteins from four HPV types: HPV 16 & 18, the types that account for about 70% of the worldwide cases of cervical cancer, and HPV 6 & 11, the types most commonly associated with genital warts.	To see whether the vaccine prevents HPV cervical infection, precancerous cervical lesions, and genital warts.	2002 NCT00092521 This trial is no longer accepting patients.
Cervical Cancer	HPV16/18 Vaccine Trial in Costa Rica	Cervarix™ HPV bivalent vaccine	National Cancer Institute (in collaboration with Costa Rican investigators)	The HPV bivalent vaccine (provided to NCI for this trial by GlaxoSmithKline Biologicals) contains viral proteins from two HPV types: HPV 16 & 18, the types that account for about 70% of the worldwide cases of cervical cancer.	To see whether the vaccine prevents persistent HPV cervical infection and precancerous cervical lesions, to examine the duration of protection seen with the vaccine, and to evaluate other issues that might increase our understanding of vaccines, immune responses to vaccines, and cervical cancer.	2004 NCT00128661 PDQ Summary (NCI-04-C-N191)
Follicular B-cell Non-Hodgkin's Lymphoma	Randomized Trial of Patient-specific Vaccination With Conjugated Follicular Lymphoma-derived Idiotype Proteins With Local GM-CSF in First Complete Remission	Biovaxid®	National Cancer Institute	The vaccine is composed of antibodies that are unique to a patient's own tumor cells. These idiotype proteins are chemically attached to the adjuvant protein keyhole limpet hemocyanin (KLH). GM-CSF (granulocyte macrophage colony stimulating factor) is used to enhance the immune response against the idiotype proteins.	To compare two vaccination groups: group I patients receive injections of the vaccine plus GM-CSF; group II patients receive injections containing only KLH and GM-CSF.	January 2000 NCT00096577 PDQ Summary (BIOVEST-BV301) This trial is currently accepting patients.
Follicular B-cell Non-Hodgkin's Lymphoma	Combination Chemotherapy Followed by Vaccine Therapy Plus Sargramostim in Treating Patients With Stage III or Stage IV Non-Hodgkin's Lymphoma	GTOP-99 MyVax® Personalized Immunotherapy	Genitope Corporation	The vaccine consists of antibodies that are unique to a patient's tumor. These idiotype proteins are chemically attached to the adjuvant protein KLH. Sargramostim (GM-CSF) is also used to enhance the	To evaluate time to tumor progression in patients who receive vaccines compared to controls, who receive adjuvant alone and GM-CSF alone.	November 2000 NCT00017290 PDQ Summary (GENITOPE-G2000-03) This trial is no longer accepting patients.

				immune response.		
Kidney Cancer	Survival Study of Oncophage® vs. Observation in Patients With Kidney Cancer	Oncophage™ (HSPPC-96)	Antigenics, Inc.	The vaccine – heat shock protein (gp96) and associated peptides – is made from each patient's own tumor.	To determine whether patients receiving Oncophage treatment for surgically removed non-metastatic renal cell carcinoma survive longer than patients who do not receive vaccine treatment.	December 2002 NCT00033904 (Part 1) PDQ Summary (C-100-12 Part I) This trial is no longer accepting patients. NCT00126178 (Part 2) This trial was terminated by the sponsor.
Cutaneous Melanoma	Study of Heat Shock Protein-Peptide Complex (HSPPC-96) vs. IL-2/DTIC for Stage IV Melanoma	Oncophage™ (HSPPC-96)	Antigenics, Inc.	The vaccine – heat shock protein (gp96) and associated peptides – is made from each patient's own tumor.	To determine whether people with metastatic melanoma who receive Oncophage after surgery live longer than people who may or may not have surgery but who receive conventional chemotherapy including interleukin-2 (IL-2)/dacarbazine /temozolomide-based therapy.	March 2002 NCT00039000 PDQ Summary (C-100-21) This trial is no longer accepting patients.
Cutaneous Melanoma	Vaccine Therapy in Treating Patients With Primary Stage II Melanoma	Not Named	European Cooperative (EORTC)	The vaccine consists of GM2, a common antigen on melanoma cells, which is conjugated to the adjuvant KLH. QS21 is used to enhance the immune response.	To compare the disease-free and overall survival of stage II melanoma patients receiving the vaccine to those not receiving the vaccine.	February 2002 NCT00005052 PDQ Summary (EORTC-18961) This trial is no longer accepting patients.
Cutaneous Melanoma	Vaccine Therapy and/or Sargramostim in Treating Patients With Locally or Advanced Metastatic Melanoma	Not Named	National Cancer Institute	The vaccine contains a combination of three melanocyte-specific antigens: tyrosinase, gp100, and MART. Sargramostim (GM-CSF) is used to enhance the immune response.	To determine the effectiveness of peptide vaccine therapy and/or GM-CSF in treating patients with locally advanced or metastatic melanoma.	December 1999 NCT00005034 PDQ Summary (ECOG-4697) This trial is currently accepting patients.
Cutaneous Melanoma	Phase III Multi-institutional Randomized Study of Immunization With the gp100: 209-217 (210M) Peptide Followed by High Dose IL-2 vs. High-Dose IL-2 Alone in Patients With Metastatic Melanoma	Not Named	National Cancer Institute	The vaccine contains gp100, IL-2, and Montanide ISA-51. Montanide ISA-51 is an oil used to enhance the immune response.	Since high-dose IL-2 is currently approved by the FDA for treating patients with metastatic melanoma, the protocol will compare the use of the vaccine plus IL-2 to IL-2 alone.	February 1999 PDQ Summary (CCCGHS-NCI-T98-0085) This trial is currently accepting patients.
Cutaneous Melanoma	MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients With Melanoma	MDX-1379	Medarex, Inc.	The vaccine contains gp100. MDX-010 is an anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody, also known as Ipilumumab. CTLA-4 helps suppress immune responses; blocking its activity with MDX-010 may improve the immune response induced by MDX-1379.	To determine the safety and effectiveness of MDX-010 in combination with MDX-1379 in patients with previously treated, unresectable stage III or IV melanoma. Survival time will be evaluated, as well as patient responses and time to disease progression.	September 2004 NCT00094653 PDQ Summary (MDX010-20) This trial is currently accepting patients
Ocular Melanoma	Vaccine Therapy in Treating Patients With Melanoma of the Eye	Not Named	European Cooperative (EORTC)	The vaccine contains several melanoma differentiation peptides.	To determine the effectiveness of vaccine therapy in preventing liver metastasis and increasing survival in patients at high risk for recurrent melanoma of the eye.	February 2002 NCT00036816 PDQ Summary (EORTC-18001) This trial is no longer accepting patients.
Prostate Cancer	GVAX® Vaccine for Prostate Cancer Versus Docetaxel and Prednisone in Patients With Metastatic Hormone-Refractory Prostate Cancer	GVAX®	Cell Genesys, Inc.	Cells from two, patient-non-specific prostate cancer cell lines that have been genetically engineered to overexpress and secrete GM-CSF, which stimulates the immune response to vaccines.	The purpose of this study is to compare the survival of patients receiving the GVAX® vaccine and the survival of patients receiving chemotherapy in individuals with prostate cancer who no longer respond to hormonal therapy, who have documented metastases, and who have not been treated with chemotherapy in the past.	July 2004 NCT00089856 PDQ Summary (G-0029, VITAL-1) This trial is currently accepting patients
Prostate Cancer	Docetaxel in Combination With GVAX ® Vaccine Versus Docetaxel and Prednisone in Prostate Cancer Patients	GVAX®	Cell Genesys, Inc.	Cells from two, patient-non-specific prostate cancer cell lines that have been genetically engineered to overexpress and secrete GM-CSF, which stimulates the immune responses to	The purpose this study is to compare the survival of patients receiving docetaxel in combination with the GVAX® vaccine versus the survival of patients receiving docetaxel and prednisone in individuals who have prostate cancer that no longer responds to hormone therapy and who have documented metastases and	July 2004 NCT00133224 PDQ Summary (G-0034, VITAL-2) This trial is currently accepting patients

				Vaccines.	cancer-associated pain.	
Prostate Cancer	Phase III Randomized Study of APC8015 (Provenge®) in Patients With Asymptomatic Metastatic Androgen-Independent Adenocarcinoma of the Prostate	Provenge® sipuleucel T	National Cancer Institute	A patient's own immune system cells trained in the laboratory to target the protein prostatic acid phosphatase (PAP), which is made by prostate cells	Compare the time to disease progression and the time to the development of disease-related pain in patients with asymptomatic, metastatic, androgen-independent adenocarcinoma of the prostate treated with APC8015 versus placebo.	March 2004 NCT00065442 This trial is currently accepting patients
Multiple Myeloma	A Study of MAGE-A3 and NY-ESO-1 Immunotherapy in Combination With DTPACE Chemotherapy and Autologous Transplantation in Multiple Myeloma.	Not Named	University of Arkansas	Fragments from two tumor proteins called MAGE-A3 and NY-ESO-1, which are found in myelomas and other tumors and which have been shown to stimulate antitumor immune responses.	Determine whether peptide vaccines will stimulate the immune system to attack and kill myeloma cells.	November 2003 NCT00090493 This trial is currently accepting patients

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